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NONINVASIVE AMBULATORY ASSESSMENT OF CARDIAC FUNCTION AND MYOCARDIAL ISCHEMIA IN HEALTHY SUBJECTS EXPOSED TO CARBON MONOXIDE

MIDTERM REPORT

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Carbon monoxide is of continuing interest to the military community. The transient nature of weapons firing, the spatial distribution of CO concentration, and differences in individual physiology will cause the CO dose to vary significantly among crewmembers. Continuous and noninvasive ambulatory monitoring of cardiopulmonary measurements in situ may provide an understanding of the effects of CO exposure among crewmembers in the field environment. This project evaluates the utility of combined impedance and electrocardiographic estimators of cardiac function during exercise in air and with exposure to CO. Treadmill exercise is included on test subjects for comparison with the existing body of data on exercise performance in asymptomatic patients and the body of data which reflects performance decrements with exercise and CO in normals. Upper body exercise is included to test the hypothesis that this form of exercise places a greater strain on the cardiovascular system than lower body exercise, both with and without CO exposure. All of the accomplished work to date has involved preparatory tasks, therefore no experimental results are reported. The midterm report does discuss the literature review, the experiment plan, and the development of a human exposure facility for executing the planned experiments.

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FOREWORD

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Paul N. Kyckelhahn — March 1, 1992

PI Signature — Date

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1.0 INTRODUCTION

1.1 Nature of the Problem

Maintenance of a high level of military capability requires that neither man nor machine be unnecessarily compromised during combat. Unfortunately, in weapons systems with closed crew compartments there are sources of risk to the human component which are only incidental to combat and are present during routine training exercises as well. These are the gaseous combustion products produced by armament propellants which enter the crew environment.

Carbon monoxide (CO), one of the toxic materials known to be produced, is of continuing interest to the military community. Although the effects on behavior and cardiopulmonary function at high CO exposure levels are fairly well documented, the effects on individuals in uncontrolled and changing exposures, such as military training and combat, are nearly impossible to predict. The transient nature of weapons firing, the spatial distribution of CO concentration, and differences in individual physiology will cause the CO dose to vary significantly among crewmembers. Furthermore, CO is only one species within the complex and dynamic chemical mixture. Continuous and noninvasive ambulatory monitoring of cardiopulmonary measurements *in situ* may provide an understanding of the effects of CO exposure among crewmembers in the field environment.

The military training environment imposes measurement difficulties which are not encountered in the typical civilian or clinical setting. Bulky protective clothing, breathing apparatus, cramped quarters, and a wide variety of postures, physical activity, and ambient conditions place severe restrictions on systems for gathering reliable cardiopulmonary information. Consequently, noninvasive measurements such as echocardiography, Doppler ultrasound, radionuclide angiography, and gas rebreathing, which serve admirably in the laboratory settings, are incompatible with field environments. Electrode-based techniques such as electrocardiography and impedance cardiography, however, could be used to assess electrical and mechanical cardiac function. In addition, they offer minimal subject intrusion and are adaptable to continuous measurement with wearable, ambulatory instrumentation.

This project evaluates the utility of combined impedance and electrocardiographic estimators of cardiac function during exercise in air and with exposure to CO. If the results of this project demonstrate that these noninvasive measurements reliably detect effects of CO exposure on cardiac performance in exercise, then the foundation for ambulatory monitoring in the field will be set.

1.2 Background of Previous Work

Carbon monoxide has been long recognized as a potentially life-threatening toxic gas and remains a common cause of mortality among poisoning victims (Sokol, 1985). The effects of carbon monoxide on respiration are considered to be threefold (Haab, 1990). The first factor is the relative carbon monoxide-oxygen affinity (M*) of various oxygen-carrying proteins including hemoglobin (M = 220), myoglobin (M = 23), and cytochrome oxidases (M = 0.5). Although carbon monoxide competes with oxygen for sites on myoglobin and cytochrome oxidases, the relatively larger affinity for hemoglobin means that carboxyhemoglobin (COHb) is often used as the primary marker of carbon monoxide exposure. In addition to reducing the number of heme sites available for oxygen, carbon monoxide augments the oxygen affinity of the oxygen-occupied sites resulting in a leftward shift in the oxygen saturation curve. This reduces the blood oxygen partial pressure (pO_2) and decreases the driving force for oxygen diffusion to peripheral tissues. Finally, recent evidence indicates that reduction in maximum oxygen consumption by exercising muscles with carbon monoxide may be linked to a decrease in the blood-to-mitochondria oxygen conductance (Haab, 1990). This is because carbon monoxide in blood may affect the off-rate kinetics of oxyhemoglobin and the carrier function of myoglobin in oxygen transport.

Several investigators have reported on the effects of carbon monoxide on submaximal and maximal exercise, and related factors such as onset of anaerobic metabolism. These papers indicate that heart rate in the presence of carbon monoxide as compared to air exposure may or may not increase at rest,

generally is higher at a given work load for submaximal exercise, and is equivalent to air exposure at maximum aerobic capacity (Vogel, 1972). Oxygen consumption, on the other hand, is generally decreased during submaximal exercise and maximal oxygen consumption is decreased compared to air exposure in proportion to the COHb concentration (Ekblom, 1972; Horvath, 1975). There is no conclusive information of the effects of carbon monoxide on stroke volume and cardiac contractility at rest or exercise, however, one could surmise that stroke volume will increase at rest to increase cardiac output when heart rate remains the same (Stewart, 1973).

The effects of carbon monoxide exposure on anaerobic threshold were reported in several studies. In normal subjects, both the time to onset of anaerobic threshold (Hirsh, 1985) and the level of oxygen consumption at which anaerobic threshold is reached were reduced. In several case studies of patients with carbon monoxide poisoning, lactate dehydrogenase was substantially elevated in those patients as compared with controls, and the amount of elevation was proportional to the duration of exposure (Sokal, 1985).

In patients with coronary artery disease (CAD), carbon monoxide exposure achieving 2-4% carboxyhemoglobin reduces time to angina in exercise, reduces time to significant ST segment depression, and in some cases, increases ST segment depression at end of exercise (Aronow, 1981; Allred, 1989 & 1991; Kleinman, 1989). Limited information also shows that CAD patients may experience a reduction in cardiac function during exercise (Adams, 1988). With CO exposures yielding a COHb of 6.0%, CAD patients increase the rate of single and multiple ventricular premature depolarizations (Sheps, 1990).

With regard to the current project, the reviewed literature brings out several important points. First, a study population of young, healthy subjects can be expected to safely exercise to maximum aerobic capacity with COHb levels under 20%. In addition, it is unlikely that these subjects will experience CO-induced arrhythmias or significant myocardial ischemia (ST segment depression greater than 0.1 mV). This is not to say, however, that sub-clinical myocardial ischemia may not arise in a slightly older, healthy population (30-40 years of age), or that such observations may not occur in some individuals over a 24-hour period post-exposure. Finally, our unique ability to noninvasively assess myocardial contractility using indices of impedance cardiography may yield new information on the exercise response of healthy subjects exposed to carbon monoxide.

1.3 Purpose of the Present Work

The goal of Study I is to demonstrate whether or not CO plus exercise can elicit measurable changes in the impedance cardiogram (ICG) in a pilot experiment. Study I will incorporate lower and upper body exercise and a wide range of CO exposure levels. Treadmill exercise is included on test subjects for comparison with the existing body of data on exercise performance in asymptomatic patients and the body of data which reflects performance decrements with exercise and CO in normals. Upper body exercise is included to test the hypothesis that this form of exercise places a greater strain on the cardiovascular system than lower body exercise, both with and without CO exposure. The a priori size of this pilot study is 20 subjects.

We will test the following hypotheses:

1) ICG acceleration exhibits a dose-response relationship to CO exposure during exercise.

2) Cardiac output exhibits a dose-response relationship to CO exposure during exercise.

3) Short-term CO exposure resulting in 5-20% COHb does not induce pathological changes in ECG rhythm or waveshape in normal subjects;

The specific objectives for Study I are:

1) To determine the effects of CO exposure on the electrocardiogram rhythm, waveshape, and ST segment level during exercise.

2) To determine the effects of CO exposure on cardiac contractility during exercise as measured by the ICG-derived aortic blood acceleration.

3) To compare certain ICG measurements of cardiac function to the more traditional measures of cardiac output, stroke volume, and oxygen consumption during exercise and CO exposure.

4) To evaluate ICG estimates of cardiac function and contractility during episodes of ECG dysrhythmia or ST segment change.

1.4 Methods of Approach

To meet the goals and objectives of this project, several major tasks were planned and undertaken:

1) Prepare a comprehensive literature review on the effects of carbon monoxide exposure on the cardiac response to exercise.

2) Prepare an experiment protocol and submit it to the RTI and U.S. Army human use review committees for approval to conduct human studies

3) Prepare a detailed experiment plan and manual of operations.

4) Acquire, prepare, calibrate, and test all necessary laboratory instrumentation and validate all data acquisition and analysis software to conduct the study.

5) Design and construct a new human exposure facility at RTI for CO research.

6) Design and construct chamber and face-mask systems for CO exposure.

7) Conduct experiments, analyze data, and report results.

This midterm report summarizes the technical approach and progress made in the tasks listed above. All of the accomplished work to date has involved preparatory tasks, therefore, no experimental studies have been conducted. Considering the potential risks and discomfort in the planned experiments, the investigators are taking great care to assure that the experimental work will be well planned; have quality instrumentation and measurements; and employ fail-safe methods and systems for carbon monoxide exposure.

2.0 TECHNICAL APPROACH AND PROGRESS

2.1 Literature Review

The objective of the literature review was to document effects of carbon monoxide exposure on the cardiac exercise response in humans. Specific topics considered were the effects of carbon monoxide exposure on cardiac function, pulmonary gas exchange, aerobic capacity, anaerobic threshold, catecholamine release, and blood lactates. The literature review comprised three sections: a summary statement of the salient reported results and their relevance to the current research project; an annotated bibliography of selected articles presented in chronological order; and a bibliography of carbon monoxide articles and other publications relevant to the current research project. The summary statement is provided in part in Section 1.2, Background of Previous Work.

2.2 Experiment Plan

2.2.1 Subject population and qualification

To minimize the variability of the subject population, we will use a narrow distribution consisting of normal, apparently healthy, males within the age range of 18-30 years. Females will not be considered because the study population is intended to reflect the population of combat tank crews; currently female soldiers are not employed in that environment. To avoid training effects, we will recruit volunteers currently engaged in some regular form of exercise such as cycling or running.

Eligibility criteria have been established to help screen participants for enrollment into the study including inclusion and exclusion criteria. Inclusion criteria have been established to help ensure optimal compliance with the study protocol and with quality control. Exclusion criteria have been established to assure that the subjects would be likely to complete the study, and that meaningful and interpretable data can be collected.

Study subjects will be recruited from various sources. Based on the potential sources as delineated below, flyers, brochures, newspaper advertisment, and contact with study personnel will publicize the program. When a person responds for enrollment, the recruitment coordinator will inform the candidate as to the enrollment procedure including qualification by medical history, physical examination, and exercise tolerance testing.

The principal investigator or other study coinvestigator will obtain written informed consent prior to initiating the experimental procedures. The subject will be informed of the nature of the procedure, its risks, its benefits, the purpose of the study, the information we will collect, and if he requests it, he will be given a summary of the data from his experiment.

Candidate subjects who have read and signed the informed consent form will come to the laboratory for initial qualification. A medical history will be taken for review of prior illness and familiar illness patterns. Each subject will then have a physical exam, with particular emphasis on screening for cardiac, cardiovascular, and respiratory illness. A blood sample will be taken and submitted for standard basic blood analyses. Subjects passing the qualification history and physical will perform an exercise tolerance test. If the subject so requests, he will receive the results of the history, physical, and exercise test when he is released from participation in the study.

2.2.2 Overview of Experiment Protocol

The study will incorporate lower and upper body exercise and a wide range of CO exposure levels. Each exercise series (lower and upper body) will comprise six replicate exercise segments designed to achieve a range of blood COHb levels. These are two AIR control exposures (0-2% COHb (endogenous or baseline level)) and four AIR + CO exposures with targets of 5% COHb, 10% COHb, 15% COHb, and 20% COHb. Each subject will serve as his own control and will experience all levels of exposure with the exposures split into two experiment days with randomization of exposure day sequence.

Subjects will be asked to eat a moderate breakfast (i.e., cereal, toast, and juice) and refrain from consuming caffeinated beverages (coffee, tea, colas) on the morning of each visit to the laboratory. Subjects will also be asked to refrain from using any prescription or over-the-counter medications after 9 pm on the evening prior to each visit to the laboratory. Subjects will report to the laboratory by 8:45 am on each of the laboratory experiment days.

On a day prior to the experiment days, each subject will participate in a training study (Table 2-1) comprising at least one exercise segment for both the upper and lower body exercise procedures. This will familiarize the subject with the experiment procedures, and determine that he is able both to exercise as prescribed and to reliably perform sham bag exposure and other breathing maneuvers.

On each day of the lower-body exercise experiments (Tables 2-2 and 2-3), the consulting physician will insert a catheter into an antecubital vein for obtaining blood samples. Then, we will instrument the subject with ECG electrodes, blood pressure cuff, and thoracic electrical impedance electrodes. After entry into the chamber, the subject will sit at rest for 15 minutes to establish stable baseline signals and to insure integrity of the venous catheter site. During this time, we will make a check of signal quality for each transducer system and begin recording cardiac physiological signals. Each subject will have his blood COHb level raised to each target level (endogenous, 5.0%, 10%, 15%, and 20% COHb) with short-term exposures (30 minute periods) while sitting at rest by inhaling precertified air and CO (up to 3000 ppm) mixtures from Douglas bags and exhaling into the exposure chamber. Blood samples will be taken at the begining of each exposure period to establish baseline COHb levels. At 5 minute intervals during bag exposure, blood samples will be taken to derive a subject-specific regression model relating COHb level to exposure duration. Exposure will be terminated when the projected COHb level is estimated to reach 95% of the target level. Blood samples will be taken again at the end of each exposure period to establish actual dose.

On each day of the upper-body exercise experiments (Tables 2-4 and 2-5), blood samples will be taken by way of venipuncture. Subject instrumentation will proceed as outlined above. As with the lower-body exposure days, each subject will have his blood COHb level raised to target levels while sitting at rest by inhaling precertified air and CO mixtures from Douglas bags and exhaling into the exposure chamber. Blood samples will be taken at the begining of each exposure period to establish baseline COHb levels. The duration of bag exposure will be estimated using the subject-specific regression model derived on the lower-body exercise day. Exposure will be terminated when the projected COHb level is estimated to reach 95% of the target level. Blood samples will be taken again at the end of each exposure period to establish actual dose.

During exercise the subject will receive a maintenance level of CO (50-100 ppm CO in chamber) to hold his COHb level relatively constant. At the end of each experiment day, we will give the subject a mixture of medical grade 95% oxygen with 5% carbon dioxide and will continue to monitor him for sixty minutes or until his blood COHb level is below 10%.

Table 2-1 Training Day.

TIME	ACTIVITY	DURATION (min)	POWER (Mets)	COHB (%)	CO (ppm)	SPEED (mph)	Elevation (% grade)
0:00	Prepare Subject	60		< 1	0		
0:59	Sham sample #1			< 1	0		
1:00	Enter Chamber	5		< 1	0		
1:05	Start Monitors	10		< 1	0		
1:14	Sham sample #2			< 1	0		
1:15	AIR Exposure	20		< 1	0		
1:34	Sham sample #3			< 1	0		
1:35	Rest, standing	5		< 1	0	0	0
1:40	Walking	5	3.7	< 1	0	2.5	3
1:45	Walking	5	6.0	< 1	0	3.5	10
1:50	Walking	5	8.5	< 1	0	5.5	10
1:55	Recovery	20		< 1	0		
2:14	Sham sample #4			< 1	0		
2:15	CO Exposure	10		< 1	0		
2:24	Sham sample #5			< 1	0		
2:25	CO Exposure	10		< 1	0		
2:34	Sham sample #6			< 1	0		

TIME	ACTIVITY	DURATION (min)	POWER (Mets)	COHB (%)	CO (ppm)	WORK (watts)
2:35	Rest, sitting	5		< 1	0	0
2:40	Cycling	5	3.7	< 1	0	50
2:45	Cycling	5	6.0	< 1	0	100
2:50	Cycling	5	8.5	< 1	0	150
2:55	Sham sample #7			< 1	0	
2:55	Recovery	20		< 1	0	
3:15	Examination	10				
3:25	Deinstrument	5				
3.30	Release					

Table 2-2. Treadmill Exercise Day 1.

TIME	ACTIVITY	DURATION (min)	POWER (Mets)	COHB (%)	CO (ppm)	SPEED (mph)	Elevation (% grade)
0:00	Prepare Subject	60		<1	0		
0:59	Blood sample #1			<1	0		
1:00	Enter Chamber	5		<1	0		
1:05	Start Monitors	10		<1	0		
1:14	Blood sample #2			<1	0		
1:15	AIR Exposure	30		<1	0		
1:44	Blood sample #3			<1	0		
1:45	Rest, standing	5		<1	0	0	0
1:50	Walking	5	3.7	<1	0	2.5	3
1:55	Walking	5	6.0	<1	0	3.5	10
2:00	Walking	5	8.5	<1	0	5.5	10
2:05	Recovery	20		<1	0		
2:24	Blood sample #4			<1	0		
2:25	CO Exposure	10		transition	1500		
2:34	Blood sample #5			transition	1500		
2:35	CO Exposure	10		transition	1500		
2:44	Blood sample #6			transition	1500		
2:45	CO Exposure	10		transition	1500		
2:54	Blood sample #7			5	100		
2:55	Rest, standing	5		5	100	0	0
3:00	Walking	5	3.7	5	100	2.5	3
3:05	Walking	5	6.0	5	100	3.5	10
3:10	Walking	5	8.5	5	100	5.5	10
3:15	Blood sample #8			5	100		
3:15	Recovery	20		5	100		
3:34	Blood sample #9			5	100		
3:35	CO Exposure	10		transition	3000		
3:44	Blood sample #10			transition	3000		
3:45	CO Exposure	10		transition	3000		
3:54	Blood sample #11			transition	3000		
3:55	CO Exposure	10		transition	3000		
4:04	Blood sample #12			15	100		
4:05	Rest, standing	5		15	100	0	0
4:10	Walking	5	3.7	15	100	2.5	3
4:15	Walking	5	6.0	15	100	3.5	10
4:20	Walking	5	8.5	15	100	5.5	10
4:25	Blood sample #13			15	100		
4:25	Recovery	20		15	100		
4:24	Observation & O_2	60					
5:45	Blood sample #14			<10	100		
5:45	Examination	10					
5:55	Deinstrument	5					
6:00	Release (3 pm)						

Table 2-3. Treadmill Exercise Day 2.

TIME	ACTIVITY	DURATION (min)	POWER (Mets)	COHB (%)	CO (ppm)	SPEED (mph)	Elevation (% grade)
0:00	Prepare Subject	60		<1	0		
0:59	Blood sample #1			<1	0		
1:00	Enter Chamber	5		<1	0		
1:05	Start Monitors	10		<1	0		
1:14	Blood sample #2			<1	0		
1:15	AIR Exposure	30		<1	0		
1:44	Blood sample #3			<1	0		
1:45	Rest, standing	5		<1	0	0	0
1:50	Walking	5	3.7	<1	0	2.5	3
1:55	Walking	5	6.0	<1	0	3.5	10
2:00	Walking	5	8.5	<1	0	5.5	10
2:05	Recovery	20		<1	0		
2:24	Blood sample #4			<1	0		
2:25	CO Exposure	10		transition	3000		
2:34	Blood sample #5			transition	3000		
2:35	CO Exposure	10		transition	3000		
2:44	Blood sample #6			transition	3000		
2:45	CO Exposure	10		transition	3000		
2:54	Blood sample #7			10	3000		
2:55	Rest, standing	5		10	100	0	0
3:00	Walking	5	3.7	10	100	2.5	3
3:05	Walking	5	6.0	10	100	3.5	10
3:10	Walking	5	8.5	10	100	5.5	10
3:15	Blood sample #8			10	100		
3:15	Recovery	20		10	100		
3:34	Blood sample #9			10	100		
3:35	CO Exposure	10		transition	3000		
3:44	Blood sample #10			transition	3000		
3:45	CO Exposure	10		transition	3000		
3:54	Blood sample #11			transition	3000		
3:55	CO Exposure	10		transition	3000		
4:04	Blood sample #12			20	100		
4:05	Rest, standing	5		20	100	0	0
4:10	Walking	5	3.7	20	100	2.5	3
4:15	Walking	5	6.0	20	100	3.5	10
4:20	Walking	5	8.5	20	100	5.5	10
4:25	Blood sample #13			20	100		
4:25	Recovery	20		20	100		
4:24	Observation & O_2	60					
5:45	Blood sample #14			<10	100		
5:45	Examination	10					
5:55	Deinstrument	5					
6:00	Release (3 pm)						

Table 2-4 Hand-Crank Exercise Day 1.

TIME	ACTIVITY	DURATION (min)	POWER (Mets)	COHB (%)	CO (ppm)	WORK (watts)
0:00	Prepare Subject	60		<1	0	
0:59	Blood sample #1			<1	0	
1:00	Enter Chamber	5		<1	0	
1:05	Start Monitors	10		<1	0	
1:15	AIR Exposure	30		<1	0	
1:45	Rest, sitting	5	1.0	<1	0	0
1:50	Cycling	5	3.7	<1	0	50
1:55	Cycling	5	6.0	<1	0	100
2:00	Cycling	5	8.5	<1	0	150
2:05	Recovery	20		<1	0	
2:24	Blood sample #2			<1	0	
2:25	CO Exposure	30		transition	1500	
2:54	Blood sample #3			5	100	
2:55	Rest, sitting	5	1.0	5	100	0
3:00	Cycling	5	3.7	5	100	50
3:05	Cycling	5	6.0	5	100	100
3:10	Cycling	5	8.5	5	100	150
3:15	Blood sample #4			5	100	
3:15	Recovery	20		5	100	
3:34	Blood sample #5			5	100	
3:35	CO Exposure	30		transition	3000	
4:04	Blood sample #6			15	100	
4:05	Rest, sitting	5	1.0	15	100	0
4:10	Cycling	5	3.7	15	100	50
4:15	Cycling	5	6.0	15	100	100
4:20	Cycling	5	8.5	15	100	150
4:25	Blood sample #7			15	100	
4:25	Recovery	20		15	100	
4:24	Observation & O_2	60				
5:45	Blood sample #8			<10	100	
5:45	Examination	10				
5:55	Deinstrument	5				
6:00	Release (3 pm)					

Table 2-5. Hand-Crank Exercise Day 2.

TIME	ACTIVITY	DURATION (min)	POWER (Mets)	COHB (%)	CO (ppm)	WORK (watts)
0:00	Prepare Subject	60		<1	0	
0:59	Blood sample #1			<1	0	
1:00	Enter Chamber	5		<1	0	
1:05	Start Monitors	10		<1	0	
1:15	AIR Exposure	30		<1	0	
1:45	Rest, sitting	5	1.0	<1	0	0
1:50	Cycling	5	3.7	<1	0	50
1:55	Cycling	5	6.0	<1	0	100
2:00	Cycling	5	8.5	<1	0	150
2:05	Recovery	20		<1	0	
2:24	Blood sample #2			<1	0	
2:25	CO Exposure	30		transition	3000	
2:54	Blood sample #3			10	3000	
2:55	Rest, sitting	5	1.0	10	100	0
3:00	Cycling	5	3.7	10	100	50
3:05	Cycling	5	6.0	10	100	100
3:10	Cycling	5	8.5	10	100	150
3:15	Blood sample #4			10	100	
3:15	Recovery	20		10	100	
3:34	Blood sample #5			10	100	
3:35	CO Exposure	30		transition	3000	
4:04	Blood sample #6			20	100	
4:05	Rest, sitting	5	1.0	20	100	0
4:10	Cycling	5	3.7	20	100	50
4:15	Cycling	5	6.0	20	100	100
4:20	Cycling	5	8.5	20	100	150
4:25	Blood sample #7			20	100	
4:25	Recovery	20		20	100	
4:24	Observation & O_2	60				
5:45	Blood sample #8			<10	100	
5:45	Examination	10				
5:55	Deinstrument	5				
6:00	Release (3 pm)					

2.3 Human Exposure Facility

At the time of the original proposal submission (August 1989), the carbon monoxide exposures were to have been conducted at facilities shared by the University of North Carolina (UNC) and the EPA Health Effects Research Laboratory, and made available to this project through the UNC subcontract. By the time the project was initiated (April 1991), these facilities were no longer available and had been partially dismantled. In response to this need, Research Triangle Institute decided to invest in a new Human Exposure Facility, thereby meeting the objectives of this project and expanding RTI's capability for human environmental exposure research.

2.3.1 General laboratory design

A floor plan of the Human Exposure Facility is presented in Figure 2-1. The principal components are the environmental exposure chamber, a changing room/airlock with sink, toilet and shower, the subject preparation area, the monitoring instrumentation area, the blood and laboratory analysis workbench, and the chamber air conditioning and control equipment. The laboratory design focused on investigator productivity, subject safety, privacy, and comfort, and emergency access.

2.3.2 Environmental exposure chamber

Chamber design began in April 1991 with a survey of the literature which describes the design and performance of existing systems at the USEPA in Chapel Hill, NC, IIT Research Institute in Chicago, IL, and others which are primarily for small-animal use.

In May 1991, RTI contracted with a local architectural design firm to develop a set of operational specifications which could be used to produce an RFP for design and construction of the exposure chamber at a preselected site within RTI. Specifications developed in this effort were released in August 1991, bids for design were received on 30 September 1991, bids for construction on 6 November 1991, and construction began on 27 January 1992.

The chamber is a single-pass air-flow design, which requires substantial heating, cooling, humidification, and dehumidification capabilities. This non-recirculating design was dictated, in part, by other potential users who are studying very low levels of volatile organic compounds (VOCs). In a recirculating design, the constraints on materials in chamber, ducting, and air-handling would have increased construction costs beyond available resources.

The system draws in outside air, passes it through both particulate and gas contaminant filters (which remove hydrocarbons, arsine, and phosphine), and then uses a closed-loop direct digital control (DDC) to achieve a prescribed flow, temperature, and relative humidity within the chamber. While the daily operating envelope of the chamber is highly dependent on the climate, the minimum envelope guaranteed for local extremes of outdoor temperature and humidity is: 65°-95° Dry Bulb; 30%-70% Relative Humidity (non-condensing); and flow rate 400-1600 cfm.

The chamber walls are two-inch thick sandwiches of polyurethane panels with interior and exterior aluminum skins (Figure 2-2, chamber under construction). Treated chamber air enters the chamber through four large diffusers in the ceiling, and exits through return ducts comprising double-panel construction on two opposing walls. Carbon monoxide (and other gaseous components) are injected into the main supply duct through a multi-port, high-pressure sparger. Concentration of carbon monoxide is controlled by a dedicated closed-loop system comprising a non-dispersive infrared (NDIR) carbon monoxide detector, a 386/25 personal computer running Control EG software[1], and a pair of mass-flow controllers. Numerous continuous comparisons of actual and calculated chamber concentrations, along with computer-independent limits, alarms, and interlocks ensure safety of both experimental subjects and operating personnel.

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[1]Quinn-Curtis, 35 Highland Circle, Needham, MA 02194

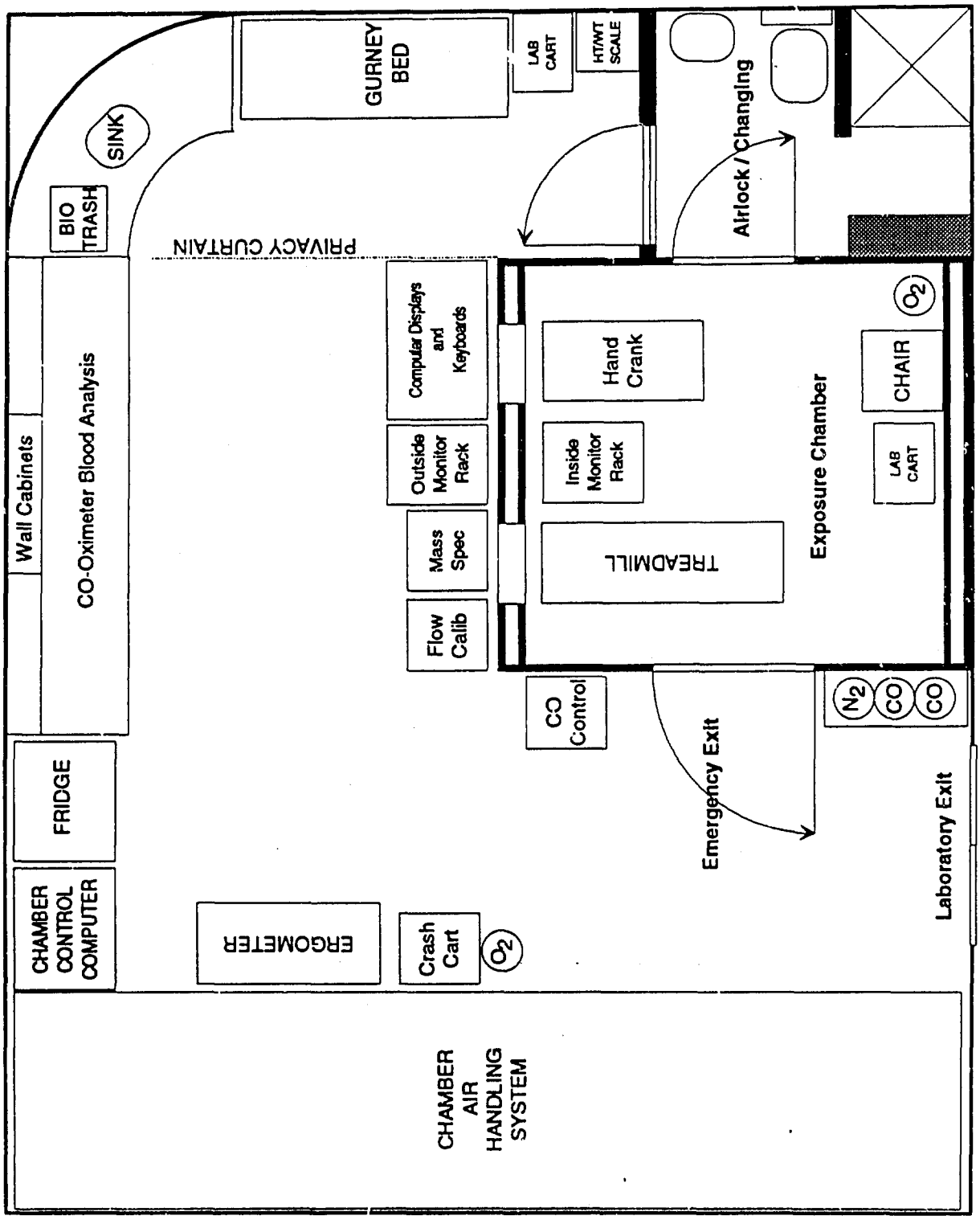

Figure 2-1. Human exposure facility floor plan.

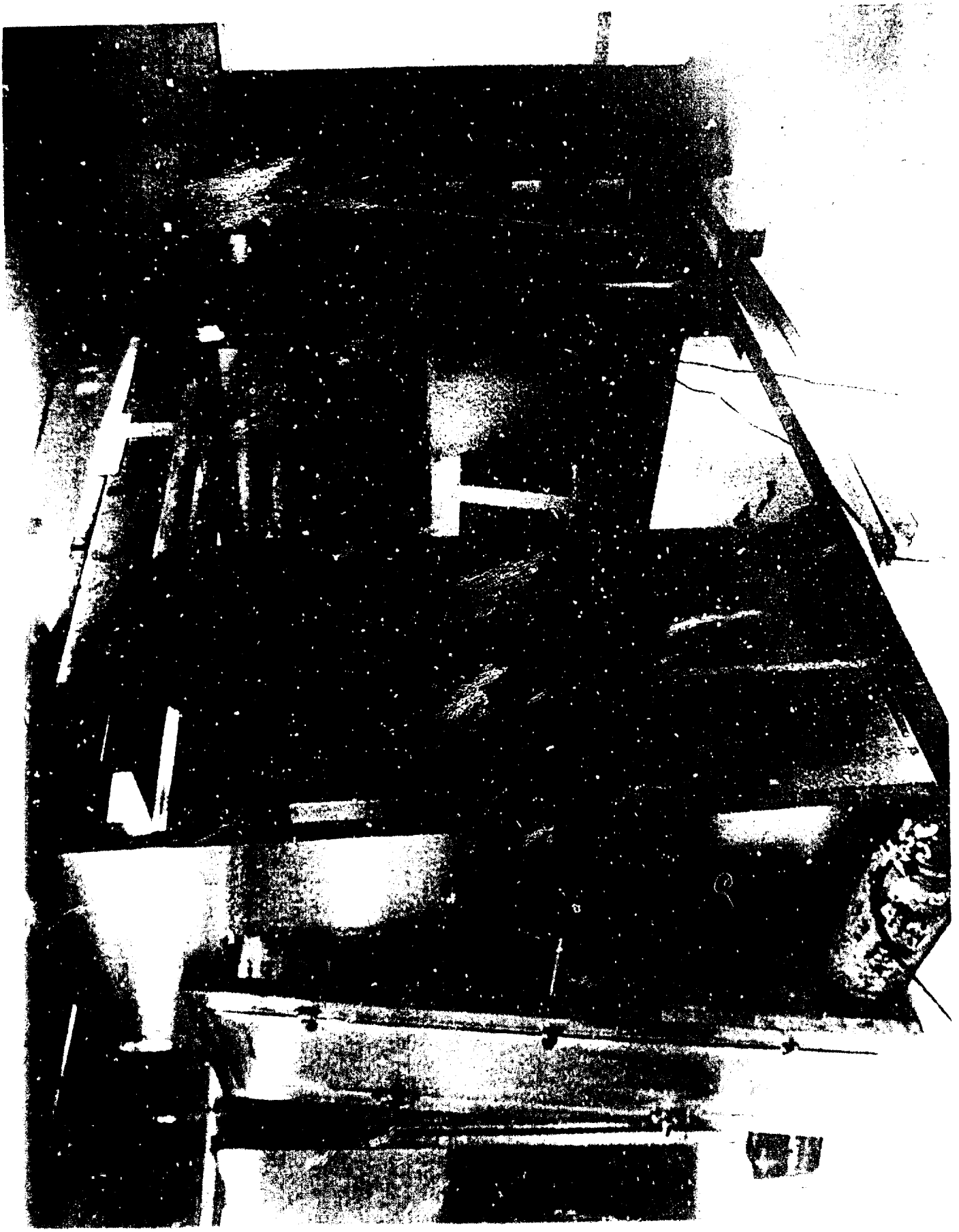

Figure 2-2. Environmental exposure chamber under construction.

2.3.3 Major equipment acquisition

RTI authorized capital equipment funds to support the new facility based upon the CO study instrumentation requirements. Acquired and planned capital equipment and minor instrumentation for the new facility include:

1) Medical Gas Analyzer, Marquette Model 1100 (mass spectrometer)
2) Treadmill, Marquette Model 1900
3) Blood Pressure Monitor, Marquette/Paramed Model 9350
4) Analog-to-Digital Subsystem, Analogic Model HDAS 16
5) Carbon Monoxide Analyzer, Rosemount/Beckman Model 800
6) Electronic Barometer, Setra Systems Model 370
7) Hematocrit Centrifuge, Clay Adams Model 556
8) Cardiac Data Acquisition Computer System, (486-based PC)
9) Pulmonary Data Acquisition Computer System, (486-based PC)
10) Chamber Environmental Control Computer System, (386-based PC)
11) Chamber CO Exposure Control Computer System, (386-based PC)
12) Chamber CO Exposure Control System

RTI has received a variety of government-furnished equipment (GFE) from the EPA inventory associated with previous USABRDL-funded projects. The major items received were:

1) CO-Oximeter, Instrumentation Laboratories Model IL282
2) Multigas Rebreathing System (physiological & electronic components)
3) Bicycle Ergometer, Collins
4) Oscillographic Recorder, Astro-Med MT8800
5) Zenith VGA display and video graphics adapter card

Several items of equipment were also acquired on project funds including:

1) SpaceLabs FT1000 Ambulatory Electrocardiogram Analyzer
2) SpaceLabs Ambulatory Electrocardiogram Recorders
3) Pacific Systems Computer System

2.3.4 Instrument control and signal data flow

A control and signal data-flow diagram for the Human Exposure Facility is presented in Figure 2-3. A variety of major subsystems, each having one or more instruments, comprise the experiment control and signal acquisition system. For chamber air conditioning (A/C), a dedicted chamber A/C controller receives input from a set of sensors and autoregulates temperature, relative humidity, and ventilation. Chamber A/C setpoints are entered via the environment control computer (ECC), which also performs data logging of all chamber variables to an archive disk file. Chamber CO level is computer-controlled (see section 2.4.1), with dual monitoring of chamber CO level, and monitoring of laboratory CO level for added safety.

The primary physiological and experiment signals (electrocardiogram, impedance cardiogram, blood pressure, temperature, and relative humidity, treadmill speed and elevation, and ergometer work load) are continuously monitored by the cardiac data acquisition computer. Continuous ECG tape recordings are also made for later analysis using the SpaceLabs arrthymia analysis computer. During rest and exercise protocol-activity segments, breath-by-breath samples of respired O_2 and CO_2 will be taken by the medical gas analyzer and their electrical analogues monitored by the pulmonary data acquisition computer. Separate breathing apparatus for the treadmill and hand-crank exercise systems are being constructed. The subject database computer manages off-line data functions including medical history, physical exam, blood hematocrit and CO-Oximeter measurements, and COHb exposure modeling.

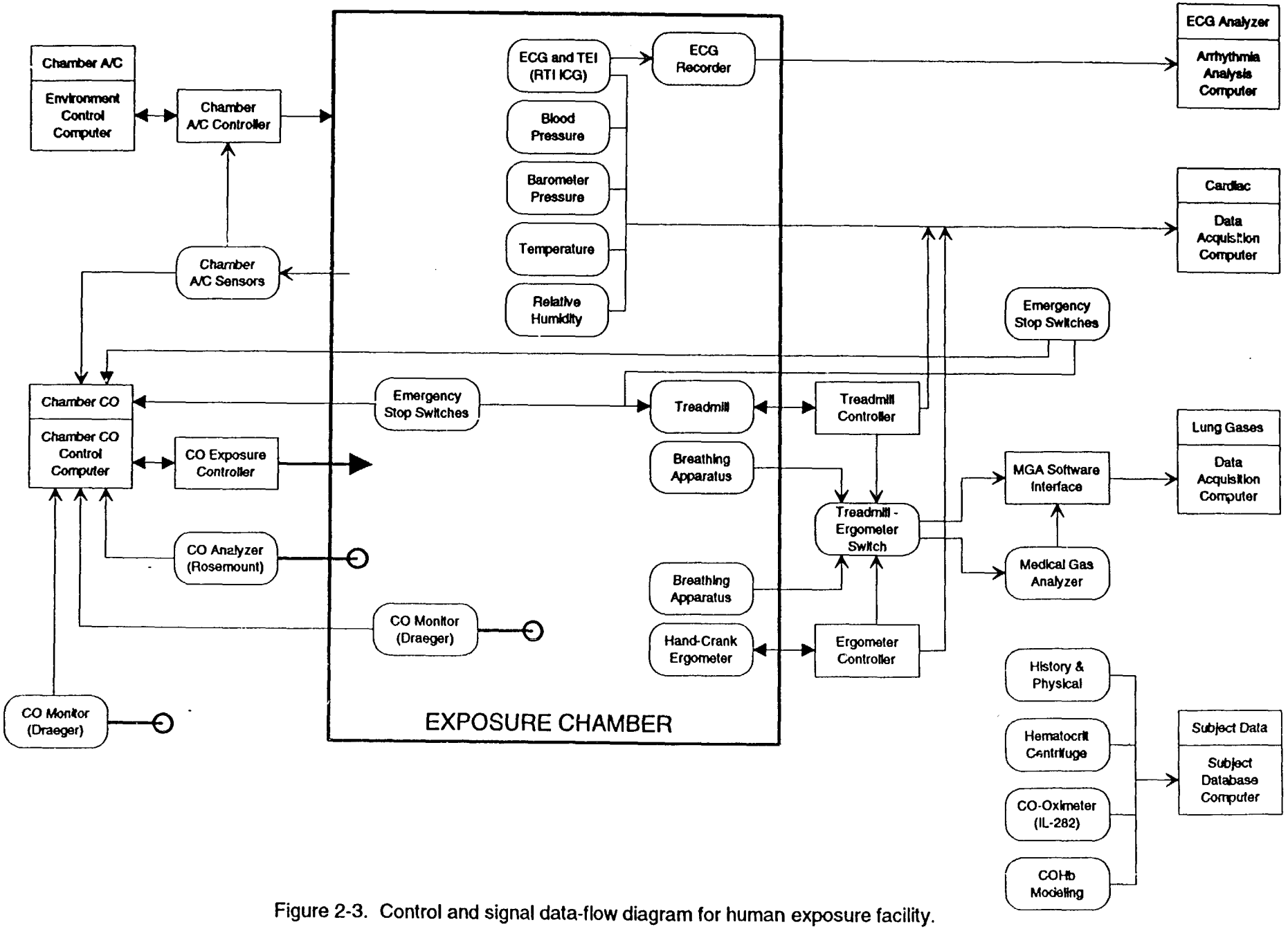

Figure 2-3. Control and signal data-flow diagram for human exposure facility.

2.4 Special Instrumentation Design and Construction

2.4.1 Chamber air and carbon monoxide exposure

The CO dosing system for the Human Exposure Facility is designed to allow chamber concentrations which range from 0 to approximately 2000 ppm. Chamber concentration, measured by a non-dispersive infrared (NDIR) spectrometer (Rosemount/Beckman Model 800), controls the flow of pure CO through a pair of mass flowmeters (MFC-1, MFC-2) which are in a software-mediated feedback loop.

The pure CO, obtained from certified bottles, is supplied at approximately 60 psig to a manifold through a two-stage regulator (Figure 2-4), the pressure relief valve of which is vented directly to the continuously-operating building exhaust. A pair of CO bottles, each with its own regulator, are connected to the manifold to reduce delays from changeout. The bottles are located in a ventilated cabinet, and a pure N_2 purge is available to flush the delivery system in an emergency or for routine maintenance and repairs. All connections to the CO manifold are protected by both normally-closed, high-pressure bellows valves and check valves on the manifold pigtails. A second set of high-pressure bellows valves route the manifold gas to either the mass flow controllers or the building exhaust.

The high-pressure bellows valves are operated by solenoid-actuated pilot valves, which in turn, are connected to the several safety systems. All of the solenoid valves in their normally-off conditions cause the bellows valves to return to states which shut off the gas supply to the manifold and release the manifold pressure to the building exhaust.

During normal chamber operation, the desired concentration of CO is continuously compared with the ratio of CO flow to chamber air flow. This ratio should always be within approximately 10% of the target concentration. If the measured ratio exceeds the nominal value by some preset value (e.g., 1.5), then there is a problem with the control loop or with the gas distribution in the chamber, and the system will be shut down. If the ratio exceeds the nominal value by a smaller amount (e.g., 1.25), for an extended period, then the system will also be shut down.

Chamber concentration is continuously measured by the NDIR instrument and by an auxiliary monitor which uses an electrochemical sensing element. Both instruments have adjustable alarm settings and are directly connected to the control system. Either instrument can interrupt the CO delivery independently of the software.

The control software must periodically reset an external "watchdog" timer to maintain CO delivery. This ensures that the mass flow controllers are always receiving a "live" signal, and that the computer which controls the feedback loop cannot simply crash with a set of output control values which are fortuitously near the desired values.

Of course, an investigator should always have the option of aborting an experiment, and manually-operated switches for this purpose are an integral part of the control system. Emergency stop switches will be located on the CO dosing system instrumentation rack, on the internal chamber instrumentation rack, and on the external chamber instrumentation rack.

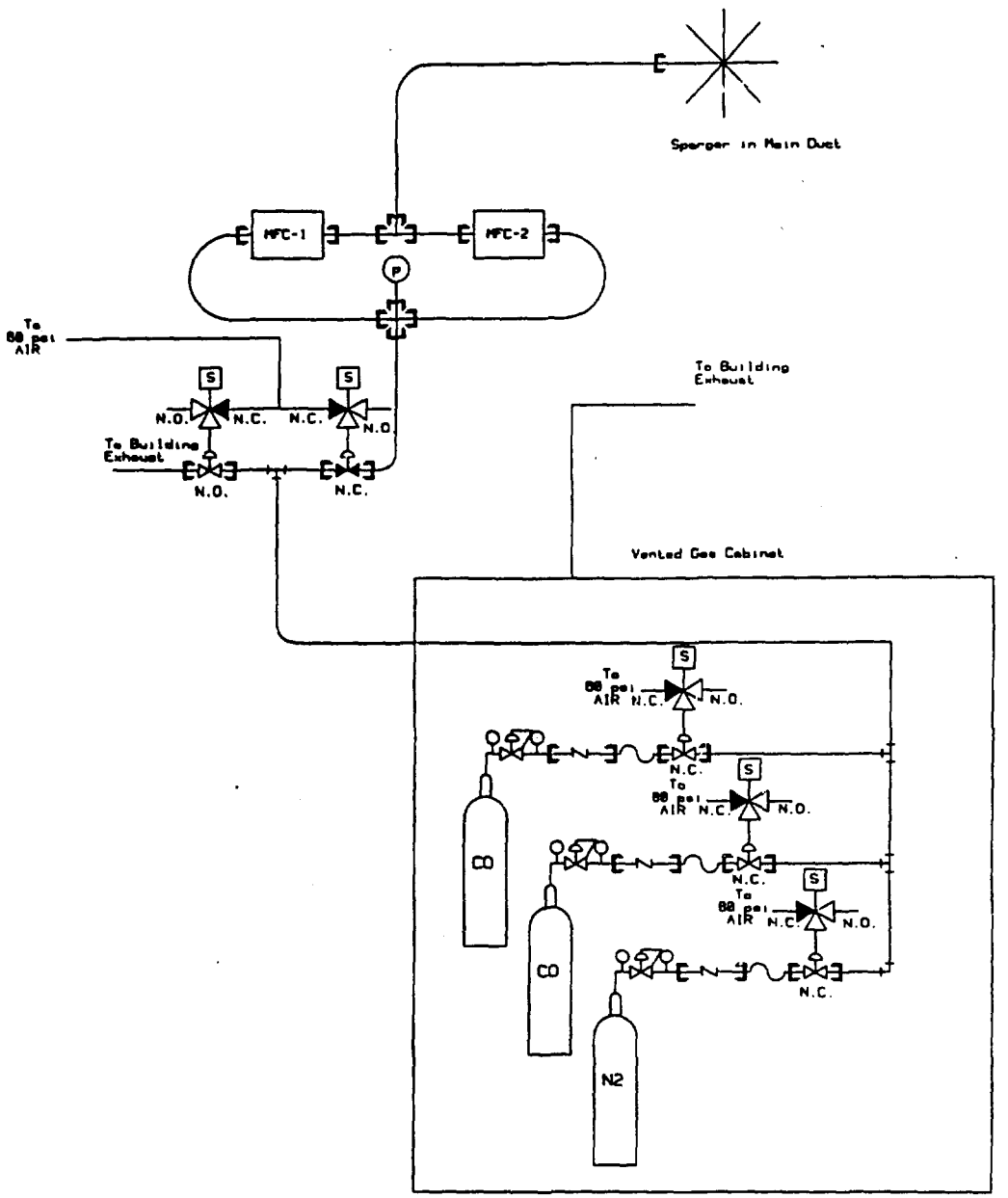

Figure 2-4. Chamber carbon monoxide dosing system.

2.4.2 Face-mask air and carbon monoxide exposure

Each subject will have his blood COHb level raised to each target level (endogenous, 5.0%, 10%, 15%, and 20% COHb) with short-term exposures while sitting at rest by inhaling precertified air and CO (up to 3000 ppm) mixtures via face-mask from Douglas bags and exhaling into the exposure chamber. The Douglas bags will be prefilled to a subject-specific volume via a mass flow meter (Scott Model 52-33C-TA1) having an integral volume totalizer and digital volume display.

2.4.3 Treadmill control and safety system

Subjects will perform lower-body exercise using a Marquette Series 1900 treadmill located inside the exposure chamber. Treadmill work load will be controlled using a Marquette Model MTC1 manual treadmill controller located outside the chamber. Emergency stop switches will be located on the treadmill handle-bar, on the internal chamber instrumentation rack, and on the external chamber instrumentation rack. Treadmill speed and elevation will be adjusted to meet the metabolic work requirements specified in the protocol as follows:

ACTIVITY	POWER (METS)	SPEED (mph)	ELEVATION (% grade)
Rest	1.0	0	0
Walking, level 1	3.7	2.5	3
Walking, level 2	6.0	3.5	10
Walking, level 3	8.5	5.5	10
Cool-down	1.5	0.7	0

2.4.4 Hand-crank ergometer construction and control

Subjects will perform upper-body exercise using a modified Collins "Pedalmate" ergometer located inside the exposure chamber. The crank mechanism was removed from the original stationary bicycle frame and attached to an apparatus suitable for hand-crank exercise. The apparatus is constructed of aluminum and comprises a 3 inch diameter vertical pipe, a 12 inch by 12 inch flange, and a 24 inch by 48 inch by 2 inch high aluminum platform (Figure 2-5). The large platform is designed for intrinsic stability, however, additional stability is gained by having the subject sit in a chair which is placed on top of the platform.

Ergometer work load will be controlled using a Collins "Total Work Integrator" manual ergometer controller located outside the chamber. Since accurate maintainence of the intended work load requires subject participation, a meter will be provided inside the chamber for visual feedback to the subject. The subject will be asked to crank the ergometer at a rate sufficient to keep the meter indicator within the "green band" on the meter scale. A second meter will be located outside the chamber for observation by the study investigator. Ergometer work load will be adjusted to meet the metabolic work requirements specified in the protocol as follows:

ACTIVITY	POWER (METS)	WORK LOAD (watts)
Rest	1.0	0
Cycling, level 1	3.7	50
Cycling, level 2	6.0	100
Cycling, level 3	8.5	150
Cool-down	1.5	25

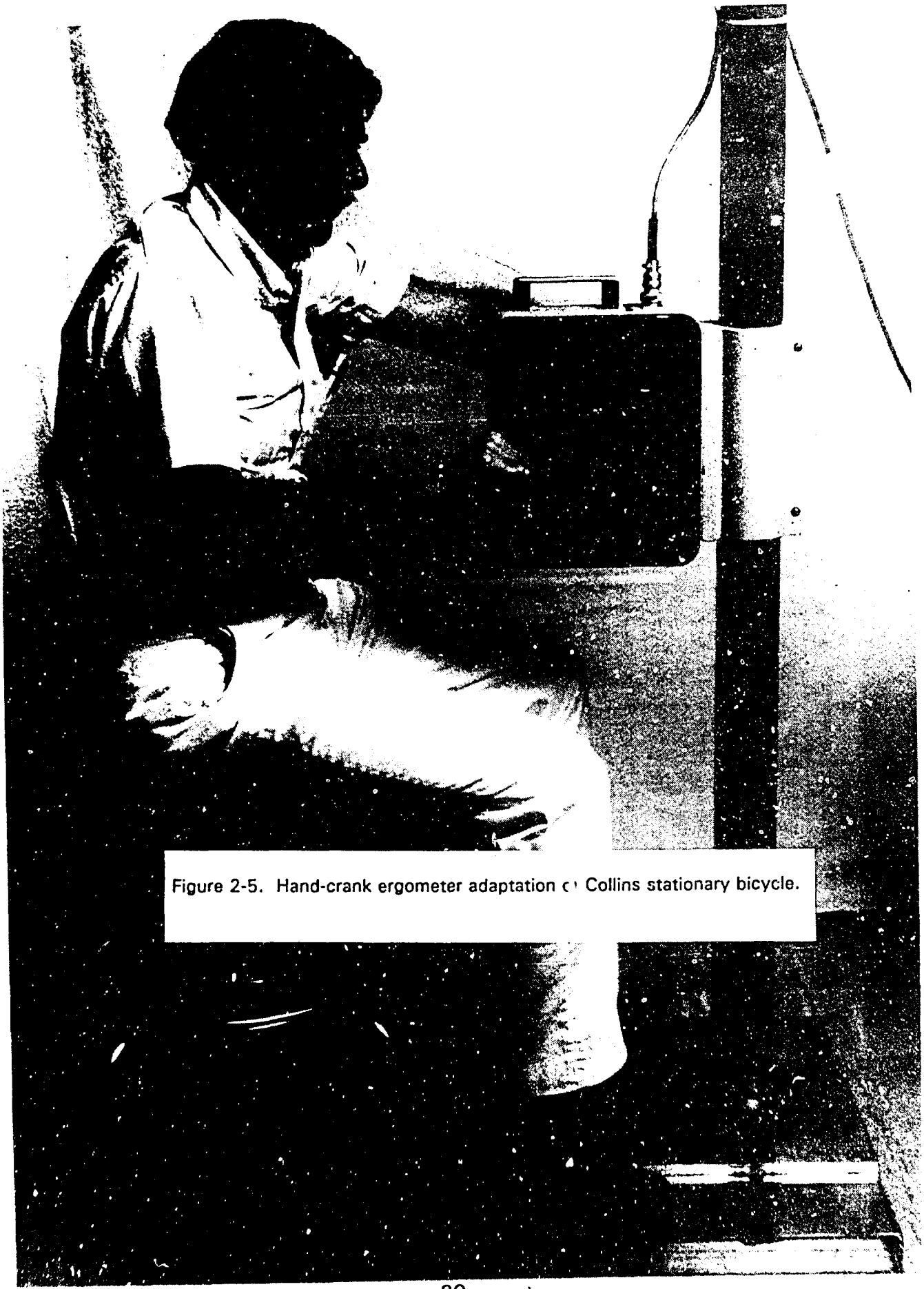

Figure 2-5. Hand-crank ergometer adaptation of Collins stationary bicycle.

2.4.5 Electrocardiograph and impedance cardiograph

For improved electrocardiogram and impedance cardiogram signal quality, a new impedance cardiograph was designed and constructed (Figure 2-6). The impedance cardiograph comprises an integrated three-channel ECG and a thoracic electrical impedance (TEI) monitor. The ECG subsystem uses an AAMI standard 5-lead patient cable and provides analog outputs for ECG leads V5, II, and aVF. Buffered low-level ECG outputs are also provided for direct connection to a SpaceLabs ambulatory ECG recorder. The TEI subsystem uses a 4-lead patient cable and provides analog outputs for Zo, ΔZ, and dZ/dt. The ECG and TEI signals, along with eight auxillary BNC input signals, will be output via a multichannel computer interface for direct connection to the analog-to-digital converter (ADC).

The new system has several design features of note. A crystal-controlled digital oscillator and a 100 kHz tuned filter are used to provide a sinusoidal current source, a driven shield is used for the current source electrode leads to maintain high output impedance, and a light-emitting diode (LED) indicates when the current source electrode impedance exceeds 100 ohms (e.g., impending contact failure). The impedance signal detector employs a 100 kHz tuned filter to supress interfering signals and a synchronous demodulator to further enhance noise immunity. The synchronous demodulator also permits selection of the magnitude, resistive, or reactive component. The electrocardiogram subsystem is designed to AAMI and American Heart Association standards for frequency response. Three ECG channels are provided: a chest lead (typically V5), a jumper-selected lead I, II, or III; and a jumper-selected lead aVF, aVR, or aVL. A summary of the general features and specifications incorporated into the RTI impedance cardiograph design is attached in Table 2-6. Also listed are comparative specifications for the traditional Minnesota ICG (Surcom, etc.) as obtained from the Minnesota ICG calibration manual.

To facilitate analysis of the ECG and TEI signals, RTI has developed the WVSHELL[2] waveform processing software system. The WVSHELL waveform processor is a comprehensive software package for acquiring, processing and analyzing sampled analog signals. Signal acquisition is managed via a user-configured protocol which specifies sampling rate, analog data channels, signal calibration, and real-time display parameters. Signal analysis is managed by programs written in WVSHELL's command language. Functions are provided for ensemble averaging, baseline correction, digital filtering, spectral analysis, waveform feature identification, timing and amplitude measurement, image printing, graphics management, and program control.

In this study, the ECG and ICG signals are sampled at 400 Hz per channel throughout the protocol. After acquisition, the acquired cardiac signals are either processed cycle-by-cycle or ensemble-averaged for a specified interval (e.g., 1 minute epochs). The cycle-by-cycle or averaged waveforms are automatically analyzed and displayed with their primary physiological measurements. These may include ST segment level and slope, systolic and diastolic time intervals, and TEI correlates of ejection velocity, acceleration, and stroke volume. These primary measurements and other measured and derived variables are stored in a dataset in either binary or comma-separated text formats.

2.5 Results and Discussion

All of the accomplished work has involved preparatory tasks and additional work must be conpleted prior to initiating human studies. Two of the major preparatory tasks (listed in section 1.4) necessary to meet the goals and objectives are complete (literature review and human studies approval) and the remaining four are progressing well. We now expect to begin human studies in the latter half of May 1992. The ultimate result of such careful and detailed preparatory work will be a high quality and fault-free experiment.

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[2]WVSHELL is a trademark of Research Triangle Institute, Research Triangle Park, NC 27709

Figure 2-6. Electrocardiograph and impedance cardiograph.

Table 2-6. Typical specifications for new RTI electrocardiograph and impedance cardiograph with comparative specifications for traditional Minnesota impedance cardiograph.

CURRENT SOURCE	RTI ECG and ICG	Minnesota ICG
Frequency	100 kHz, sinusoidal	100 kHz, sinusoidal
Output level	1 mA rms	4 mA, rms
Effective output impedance*	100 kohm	40 kohm
Linear driving range**	0 ohm to 10,000 ohms	
Maximum open circuit output	± 14 V	

*Driven shield on output to maintain high output impedance
**Current source LED indicates when output impedance exceeds 100 ohms

Zo CHANNEL (magnitude, resistive, or reactive component)		
Input range	0 ohms to 80 ohms	10 ohms to 80 ohms
Bandwidth (-3dB)	DC to 0.07 Hz, 100 Hz optional	
Noise	16 mohms peak-to-peak	
Output sensitivity	125 mV/ohm	
Resolution (16 bit ADC)	2.44 mohms/LSB	6.1 mohms/LSB
Front panel digital display		

ΔZ CHANNEL	
Input range	± 2 ohms (Rebalance OFF)
Bandwidth (-3dB)	DC to 100 Hz
Noise	1.6 mohms peak-to-peak
Output sensitivity	5.0 V/ohm
Resolution (16 bit ADC)	0.061 mohms/LSB

ΔZ REBALANCE	
Rebalance threshold	± 1.80 ohms
Residual Zo component	0.0 ± 5.0 mohms
Droop rate	1.2 mohms/s
Manual rebalance pushbutton	
Rebalance LED indicates when manual or automatic rebalance occurs	

dZ/dt CHANNEL		
Input range	± 4 ohms/s	± 6 ohms/s (estimate)
Bandwidth (-3dB)	2 Hz to 40 Hz	N/A to 40 Hz
Noise	4.0 mohm/s peak-to-peak	200 mohm/s p-p
Output sensitivity	2.5 V/ohm/s	0.50 V/ohm/s
Resolution (16 bit ADC)	0.019 mohms/s/LSB	1.22 mohms/s/LSB

ECG CHANNELS (V5, II, aVF)		
Input range	± 5 mV	Non-standard ECG
Bandwidth (-3dB)	0.05 Hz to 106 Hz	
Noise	4 μ V peak-to-peak	
Output sensitivity	2000 V/V	
Resolution (16 bit ADC)	0.159 μ V/LSB	

OTHER	
Eight auxiliary analog input channels for WVSHELL data acquisition and analysis	
Typical leakage current, total instrument	11 μ A rms
Typical lead leakage current to ground	6 μ A rms
Typical isolated lead leakage current to ground	17 μ A rms

3.0 CONCLUSIONS

Since the experimental work in this study has not yet started, new insights into the problen of combined carbon monoxide exposre and exercise are limited. The best information to date arises from the reviewed literature and annotated bibliography.

In spite of the number and variety of articles on the effects of carbon monoxide on exercise in humans, many unanswered questions remain or have not been thoroughly explored. Little information is available, for instance, regarding the effects of high levels of carbon monoxide (e.g., 15-20%) on cardiac functional performance and exercise. In particular, it would be interesting to investigate whether changes in cardiac contractility from one level to another level of exercise is affected by substantial CO exposure, and whether or not such effects are influenced by age, sex, or aerobic fitness. Aside from the well-researched effect of carbon monoxide on maximum aerobic capacity, effects on other aspects of cardiovascular physiology are less known. For instance, no information is available on the relationship between rate of accumulated carbon monoxide dose and cardiopulmonary function or exercise capacity.

Another important question is whether or not carbon monoxide exposure may induce orthostatic intolerance in healthy subjects, or increase intolerance in susceptable populations. Neural mechanisms regulating cardiovascular function during orthostatic stress may be more compromised than the myocardium especially when COHb is less than 10%, thereby reducing the cardiovascular response in spite of adequate cardiac reserve. Since orthostatic intolerance affects a significant fraction of the young adult population, these effects may be more likely to induce syncope than myocardial collapse in the typical military population.

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